Clinical Infectious Diseases

MAJOR ARTICLE

Systematic Review and Meta-analysis of the Association Between *Mycoplasma Genitalium* and Pelvic Inflammatory Disease (PID)

Kay Htaik,[1,2] Lenka A. Vodstrcil,[1,2,3] Erica L. Plummer,[1,2] Amelia M. Sfameni,[2] Dorothy A. Machalek,[4,5] Lisa E. Manhart,[6] and Catriona S. Bradshaw[1,2,3]

[1]Melbourne Sexual Health Centre, Alfred Health, Melbourne, Victoria, Australia; [2]School of Translational Medicine, Monash University, Melbourne, Victoria, Australia; [3]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia; [4]Centre for Women's Infectious Diseases, The Royal Women's Hospital, Parkville, VIC, Australia; [5]The Kirby Institute, University of New South Wales, Kensington, Sydney, NSW, Australia; and [6]Departments of Epidemiology and Global Health, Center for AIDS and STD, University of Washington School of Public Health, Seattle, Seattle, Washington, USA

Background. Differences in opinion concerning the contribution of *Mycoplasma genitalium* to pelvic inflammatory disease (PID) has resulted in inconsistencies across global testing and treatment guidelines. We conducted a systematic review and meta-analysis to determine the association between *M. genitalium* and PID and *M. genitalium* positivity within PID cases to provide a contemporary evidence base to inform clinical practice (PROSPERO registration: CRD42022382156).

Methods. PubMed, Embase, Medline, and Web of Science were searched to 1 December 2023 for studies that assessed women for PID using established clinical criteria and used nucleic acid amplification tests to detect *M. genitalium*. We calculated summary estimates of the (1) association of *M. genitalium* with PID (pooled odds ratio [OR]) and 2) proportion of PID cases with *M. genitalium* detected (pooled *M. genitalium* positivity in PID), using random-effects meta-analyses, with 95% confidence intervals (CI).

Results. Nineteen studies were included: 10 estimated *M. genitalium* association with PID, and 19 estimated *M. genitalium* positivity in PID. *M. genitalium* infection was significantly associated with PID (pooled OR = 1.67 [95% CI: 1.24–2.24]). The pooled positivity of *M. genitalium* in PID was 10.3% [95% CI: 5.63–15.99]. Subgroup and meta-regression analyses showed that *M. genitalium* positivity in PID was highest in the Americas, in studies conducted in both inpatient and outpatient clinic settings, and in populations at high risk of sexually transmitted infections.

Conclusions. *M. genitalium* was associated with a 67% increase in odds of PID and was detected in about 1 of 10 clinical diagnoses of PID. These data support testing women for *M. genitalium* at initial PID diagnosis.

Keywords. pelvic inflammatory disease; *Mycoplasma genitalium*; meta-analysis; systematic review; women's health.

Pelvic inflammatory disease (PID) is common among women of reproductive age and associated with adverse reproductive health sequelae including tubal factor infertility, chronic pelvic pain, and ectopic pregnancy [1]. Chlamydia and gonorrhea are 2 common causes of PID but are often only detected in up to 30% of cases [2]. Data that implicate other infections as a cause, such as *Mycoplasma genitalium*, are more limited. An earlier systematic review and meta-analysis published in 2015 including 10 studies found that *M. gentialium* was associated with 2-fold increased odds of PID (pooled odds ratio [OR] = 2.14; 95% confidence interval [CI]: 1.31–3.49, $I^2 = 51.3\%$) [3]. However, international guidelines vary in their recommendations regarding testing for *M. genitalium* in PID, and expert opinion differs as to whether *M. genitalium* is a significant cause of PID. For example, the World Health Organisation (WHO), Australian and UK guidelines recommend testing for *M. genitalium* at first presentation with symptoms consistent with PID [4–6]. The US Centers for Disease Control and Prevention (CDC) PID guidelines state that the value of testing women with PID for *M. genitalium* is unknown, but the CDC *M. genitalium* specific guidelines state that *M. genitalium* testing should be considered among women with PID [7]. A contemporary understanding of the contribution of *M. genitalium* to PID and its prevalence in women with suspected PID is clearly needed to inform current clinical practice and policy and create consistency across guidelines for clinicians.

Current recommendations for the treatment of PID include antibiotics such as doxycycline, ceftriaxone and metronidazole

Received 20 March 2024; editorial decision 18 May 2024; published online 7 June 2024

Correspondence: K. Htaik, Melbourne Sexual Health Centre, 580 Swanston St, Carlton, VIC 3053, Australia (kay.htaik@monash.edu); C. S. Bradshaw, Melbourne Sexual Health Centre, 580 Swanston St, Carlton, VIC 3053, Australia (catriona.bradshaw@monash.edu)

Clinical Infectious Diseases®

https://doi.org/10.1093/cid/ciae295

that target known aetiologic pathogens including chlamydia, gonorrhea, and anaerobes [8]. Although recent data suggest metronidazole in combination with doxycycline may have modest efficacy against *M. genitalium* [9], antibiotics with higher efficacy against *M. genitalium* are often needed to achieve cure. We undertook a systematic review and meta-analysis of studies published to 1 December 2023 to determine the association between *M. genitalium* and PID and *M. genitalium* positivity within PID cases diagnosed with established clinical criteria, to generate a contemporary evidence base to inform optimal clinical practice for PID.

METHODS

Study Design and Protocol

This review was guided and reported according to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement [10] (Supplementary Tables 1 and 2). Analysis methods and inclusion criteria were specified in advance and the review protocol was prospectively registered with PROSPERO (ID: CRD42022382156; http://www.crd.york.ac.uk/PROSPERO/).

Data Sources and Searches

We searched all human studies published in English before 1 December 2023 that reported on *M. genitalium* and PID. Studies were identified from electronic databases (PubMed, EMBASE, OVID MEDLINE, and Web of Science) using search terms that incorporated "*mycoplasma genitalium*" and "pelvic inflammatory disease" or related terms (Supplementary Table 3).

Eligibility Criteria

Studies were eligible if they (1) assessed PID in women using established clinical criteria outlined in the national guidelines (eg, European, Australian, US-CDC, UK-BASHH, and Hager's diagnostic criteria [4, 5, 7, 11, 12]) or had histologically confirmed endometritis or had a laparoscopic diagnosis of salpingitis; (2) included at least 10 PID cases; and (3) tested for *M. genitalium* using nucleic acid amplification tests (NAAT). All study designs (ie, case-control, cross-sectional, retrospective, and prospective) and study settings were included. Studies were excluded if they used serology for *M. genitalium* detection or did not use an established diagnostic method for PID (eg, reported a diagnosis of PID without noting how this was defined). Conference abstracts and review articles were excluded.

Study Selection and Data Extraction

Two researchers (K. H., A. S.) independently screened study titles and abstracts from the database search. Potentially eligible studies underwent full-text screening against stated criteria, documenting reasons for exclusion. Data extraction was conducted by K. H. and reviewed by A. S., with discrepancies resolved by a third researcher (E. P., L. V., C. B.). In cases of multiple publications on the same population, priority was given to studies primarily investigating the *M. genitalium*-PID association or those with the most comprehensive data. Extracted data included publication details, study design and population characteristics, specimen type and *M. genitalium* diagnostic methods, PID outcome definition, *M. genitalium* outcome data, adjusted factors in analyses, coinfections, and relevant clinical features/complications. Eleven authors were contacted for additional data clarification, with 7 responses received.

Outcome and Outcome Measures

The primary outcome measure was an estimate for the association between *M. genitalium* and PID reported as pooled OR with 95% CIs. The secondary outcome was an estimate of *M. genitalium* positivity within PID cases reported as a pooled proportion with 95% CIs.

Data Analysis

We analyzed the data using STATA v17 (StataCorp LP, College Station, Texas, USA) and calculated outcome measures using a random-effects model. Adjusted ORs were used in pooled estimates where available; otherwise, unadjusted ORs were used or calculated from extracted data. *M. genitalium* positivity among all PID cases was calculated from raw data extraction. Heterogeneity between studies was assessed using the I^2 statistic, with values <25%, 25%–75%, and >75% indicating low, medium, and high heterogeneity, respectively.

We undertook subgroup analyses and univariable random effects meta-regression by broad geographic regions, study setting and study population to investigate potential sources of heterogeneity. We used WHO-defined regions for countries in which studies were conducted. Studies were stratified by different clinical settings which included obstetrics and gynecology clinics, sexual health clinics, and mixed clinic settings (defined as a mix of outpatient/inpatient/emergency clinics). Study population groups were defined as higher epidemiological risk of sexually transmitted infections (STI) than the general population based on demographic data. Studies that included mainly young adolescents, sex workers, or African American women were deemed higher risk populations. A sensitivity analysis was conducted to assess the impact of outlier studies on summary estimates, defining outliers as those with 95% CIs lying outside the pooled estimate's 95% CI [13].

Risk of Bias and Quality Assessment

For the primary outcome, publication and small study bias was assessed using funnel plots of proportions against sample sizes and the Egger's test. To evaluate within-study bias across publications, we adapted the instrument by Hoy et al, which examines the internal and external validity of selected studies [14] (Supplementary Table 4). The tool consisted of eight questions and reported (i) representation of the general population,

(ii) representation of target population, (iii) whether study population samples were randomly selected, (iv) whether a cervicovaginal sample was used for *M. genitalium* diagnosis, (v) whether the same mode of data collection was used for all participants, (vi) primary or secondary analysis, (vii) whether power/sample size calculations were reported, and (viii) whether the analyses were adjusted for confounding variables. For each question, studies were given a score of 0 (low risk), 1 (medium risk), or 2 (high risk). Two reviewers (K. H., A. S.) independently assessed the risk of bias of each study with differences resolved by discussion with a third author (E. P., L. V., C. B.). Studies were not excluded based on the risk of bias assessment.

RESULTS

Study Selection

The search process and selection of studies is demonstrated in Figure 1, and included studies are summarised in Table 1. The initial search identified 1932 studies. After excluding 857 duplicates, 1075 studies underwent title and abstract screening. Of these, 1035 were not relevant and excluded, leaving 40 studies for full-text review. Twenty-one studies were excluded following full-text review. Reasons for exclusion included: PID not diagnosed using established criteria (n = 9), study included <10 PID cases (n = 4), reported on the same population as an included study (n = 4), and insufficient data for analysis or authors failed to respond after 3 attempts at contact (n = 4). Overall, 19 studies underwent data extraction and were included in analyses.

Study Characteristics

Table 1 presents characteristics of the 19 included studies, conducted between 2002 and 2022, with sample sizes ranging from 34 to 2378, providing a pooled sample size of 21 104 women. Using the WHO-defined regions, 7 studies (37%) were from the European region, 5 (26%) from the Americas, 4 (21%) from the Western Pacific region, and 3 (16%) from the African region. There were 4 case-control studies, 7 cross-sectional studies, 2 prospective studies, 4 retrospective studies, and 2 randomized controlled trials (RCTs). Seven studies were conducted in STI clinics, 6 in mixed settings (outpatient/inpatient/emergency), 4 in obstetrics and gynecology clinics, and 1 each in a family planning clinic and among university students. The study participant ages ranged from 13 to 67 with most studies (n = 15) using established clinical criteria for PID diagnosis, 3 using histological confirmation of endometritis, and 2 using laparoscopic confirmation of salpingitis.

Across the 19 studies, *M. genitalium* prevalence among women ranged from 0.41% [15] to 45% [16]. The highest prevalence was in an RCT among adolescents and young adults with mild-moderate PID symptoms in the United States in 2021 [16], whereas the lowest prevalence was among women over 15 years old presenting with PID signs or symptoms to a gynecology department in Hungary in 2003 [15].

Estimate of the Association Between *M. genitalium* and PID

Of the 19 included studies, 10 [17–26] (7246 people) were eligible for the primary outcome. *M. genitalium* was significantly associated with PID with a pooled OR of 1.67 (95% CI: 1.24–2.24, $I^2 = 32.2\%$; Figure 2). Of the 10 studies, 4 (40%) were from the European region, 3 (30%) from the Americas, 2 (20%) from the African region, and 1 (10%) from the Western Pacific region. For 2 studies, we used published adjusted OR, 1 adjusted for age and chlamydia coinfection [17], and the other adjusted for age, race, and chlamydia and/or gonorrhea coinfection [20]. For the other 8 studies, the OR was generated using raw extracted data. Subgroup analysis was not performed due to low heterogeneity.

Pooled Positivity of *M. Genitalium* Within PID Cases

Nineteen studies [9, 15–32] contributed to the pooled summary estimate (SE) of 10.3% (95% CI: 5.63–15.99, $I^2 = 95.51\%$) of *M. genitalium* within PID cases (Figure 3). To explore the high heterogeneity, we conducted subgroup analyses and meta-regression based on WHO geographic region, study setting and study population groups. We found the highest proportion of *M. genitalium* in PID was in the Americas (pooled SE = 15.44%) and African regions (pooled SE = 12.61%) compared to the European region (pooled SE = 6.32%; Supplementary Figure 1 and Supplementary Table 5). Similarly, STI clinics and mixed clinical settings showed higher proportions compared to obstetrics and gynaecology clinics (Supplementary Figure 2). Women with PID at higher risk of STIs had a higher prevalence of *M. genitalium* (pooled SE = 13.79%) compared to those at lower risk (pooled SE = 8.14%). Although the differences in these sub-groups may have contributed to some of the heterogeneity seen, it remained high. A sensitivity analysis that excluded 4 outlier studies (studies with estimates and 95% CIs that lay outside of the 95% CIs of the pooled estimate) showed a pooled positivity of 9.61% (95% CI: 6.83–12.77, $I^2 = 70.51\%$), similar to the overall estimate (Supplementary Figure 3).

Between-study Bias

Between-study bias assessment was conducted for the association between *M. genitalium* and PID (ie, primary outcome). The funnel plot showed symmetry and indicated no small study effects (Supplementary Figure 4). There was no evidence of publication bias by the Egger's test, with a coefficient of 0.55 ($P = .573$).

Within-study Bias

Supplementary Table 6 provides the risk of bias assessment for all studies. Seven studies were assessed as high risk of bias as the

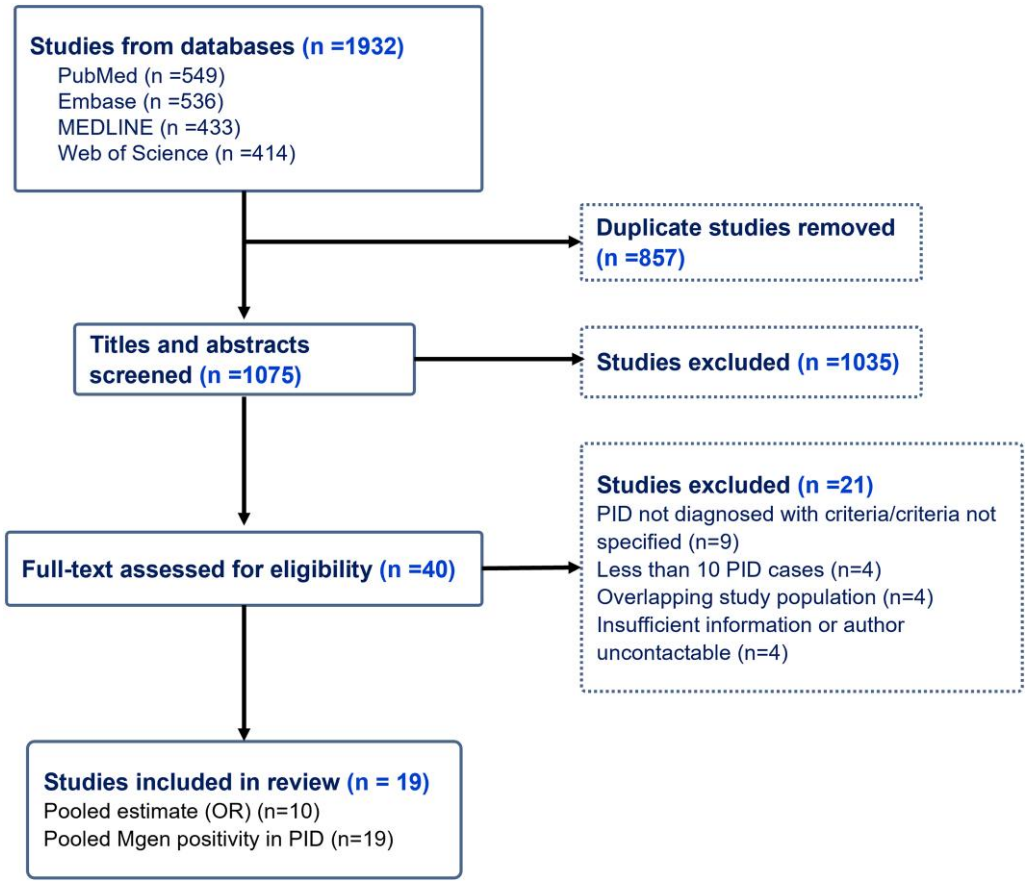

Figure 1. Flow diagram of studies included in meta-analysis of the association between *Mycoplasma genitalium* and PID. Abbreviations: OR, odds ratio; Mgen, *M. genitalium*; PID, pelvic inflammatory disease.

study population was deemed to be at high epidemiological risk of STIs based on demographic data (eg, race, age, or sex work). Four studies were deemed at risk of bias because they did not report sample type (n = 1) or used a mixture of cervicovaginal and/or urine samples (n = 3) and urine is a less sensitive sample for *M. genitalium* detection. Most studies (n = 16) were underpowered or did not report power/sample size calculations.

DISCUSSION

This systematic review and meta-analysis found that *M. genitalium* was associated with a 67% increase in the odds of PID (pooled OR 1.67 [95% CI: 1.24–2.24]), and *M. genitalium* was detected in 1 of 10 women diagnosed with PID by established criteria (pooled estimate of 10.3% [95% CI: 5.63–15.99]).

Our estimate for the association between *M. genitalium* and PID is slightly lower and has tighter confidence intervals than the pooled estimate previously reported by Lis et al in 2015 (pooled OR = 2.14; 95% CI: 1.31–3.49, $I^2 = 51.3\%$) [3]. Importantly, in the prior meta-analysis, 3 of 10 included studies used serology to detect *M. genitalium*, which is not sensitive or specific for the acute diagnosis of *M.genitalium*. When these studies were removed the pooled estimate actually increased to 2.73 (95% CI: 1.60–4.66]) [3]. Another meta-analysis of 2 prospective studies examined the association between *M. genitalium* and incident PID and reported a pooled risk ratio of 1.73 (95% CI: .92–3.28), similar to our estimate with wider confidence intervals [33]. It is important to note that Cina et al recalculated the estimate for the Haggerty 2008 which resulted in the lower pooled risk ratio. As no new prospective studies had been conducted since this previous meta-analysis, we did not perform another subgroup analysis of prospective studies.

Our pooled summary estimate of *M. genitalium* positivity within PID cases was 10.3% (95% CI: 5.63–15.99, $I^2 = 95.51\%$). Published population-based studies in the United Kingdom and United States suggest that *M. genitalium* has an estimated pooled prevalence of 1%–2% among women in the general population [34–36]. Our study suggests the positivity of *M. genitalium* in women with PID is ≥5-fold higher than reported in population estimates and within the range reported for chlamydia in women with PID (6.60% to 20.0%) [37, 38].

Table 1. Studies With Data on the Association Between *Mycoplasma genitalium* and PID (n = 19)

Author (Year of Publication)	Country (WHO Region)	Study Design	Study Population	Setting	PID Diagnosis Criteria	Sample Type	Analysis Included for Mg-PID Association or Mg Positivity
Sweeney et al (2022) [31]	Australia	Retrospective	PID-diagnosed patients	Family planning clinics	European and AUS STI management guidelines	Endocervical swabs[a]	Mg positivity
Yagur et al (2021) [32]	Isarel	Retrospective	PID-diagnosed patients	Inpatient and outpatient gynaecology clinic	CDC diagnostic criteria[b]	Endocervical swabs	Mg positivity
Wiesenfeld et al (2021) [9]	USA	RCT	Women presenting with acute PID	Emergency departments, STI clinic	CDC diagnostic criteria	Endocervical swabs and endometrial tissue	Mg positivity
Trent et al (2021) [16]	USA	RCT	Adolescent young adults with mild or moderate PID	Primary, acute, emergency department	CDC diagnostic criteria	Self-collected vaginal swab samples and vaginal cup specimens	Mg positivity
Spiller et al (2020) [25]	UK	Cross sectional Case-control	STI clinic attendees	STI clinics	BASHH and RCOG guidelines	Urine and/or (urethral, endocervical or high vaginal swabs)	Mg-PID association and Mg positivity
Ovens et al (2020) [30]	UK	Retrospective	STI clinic attendees	STI clinics	Pelvic pain, tenderness on bimanual examination, other causes had been excluded	No Information	Mg positivity
Haggerty et al (2020) [19]	USA	Case-control	Family planning, gynaecology clinics, STD units and university outpatient clinic	Mixed Setting, GIFT cohort	PID confirmed by histology of endometrial biopsy	Vaginal swabs	Mg-PID association and Mg positivity
Beesley et al (2019) [27]	Australia	Retrospective	Inpatient and outpatient attendees	Hospital	Australian STI guidelines	Vaginal swabs[a]	Mg positivity
Lillis et al (2019) [21]	USA	Cross sectional	Non pregnant/not taken an antibiotic in the last 3 months	STI clinic	Pain on palpation of pelvic abdomen, cervical motion tenderness, or adnexal tenderness	First void urine samples and vaginal samples	Mg-PID association and Mg positivity
Goller et al (2017) [29]	Australia	Cross-sectional	New female, non-sex worker patients	STI clinic	Minimum criteria of uterine, cervical motion or adnexal tenderness	Urine, high vaginal or cervical swabs	Mg positivity
Oliphant et al (2016) [23]	New Zealand	Cross-sectional Case-control	Women attending the STI clinics	STI clinic	Minimum findings of either cervical motion tenderness or uterine or forniceal tenderness on bimanual examination	Cervical swabs (frozen)	Mg-PID association and Mg positivity
Vandepitte et al (2012) [26]	Uganda	Cross-sectional	Sex workers/entertainment industry	STI clinic	Lower abdominal pain confirmed by bimanual palpation	Stored sample of endocervical swabs	Mg-PID association and Mg positivity
Oakeshott et al (2010) [22]	UK	Prospective cohort	University female students, sexually active, not pregnant, had not been tested for C. Trachomatis	University students	Modified Hager's clinical criteria and CDC criteria	Stored vaginal samples	[c]Mg-PID association and Mg positivity
Bjartling et al (2010) [17]	Sweden	Case-control	Women seeking termination of pregnancy	Gynaecology outpatient	CDC diagnostic criteria	Urine with cervical samples (or) urine with vaginal samples	Mg-PID association and Mg positivity

Table 1. Continued

Author (Year of Publication)	Country (WHO Region)	Study Design	Study Population	Setting	PID Diagnosis Criteria	Sample Type	Analysis Included for Mg-PID Association or Mg Positivity
Haggerty et al (2008) [20]	USA	Cross sectional, prospective cohort	Non-pregnant, women who are clinically suspected of PID	Mixed setting	Endometritis: modified criteria by Kiviat et al.	Stored cervical and endometrial samples	[d]Mg-PID association and Mg positivity
Cohen et al (2005) [28]	Kenya	Case-control (defined by HIV status)	Women presenting with clinically suspected PID	Hospital attendees with suspected PID	Laparoscopic diagnosis	Frozen samples cervical swabs	Mg positivity
Skapinyecz et al (2003) [15]	Hungary	Cross-sectional	Women presenting with signs or symptoms of acute PID	Hospital gynaecological department	Clinical and laparoscopic criteria	Cervical and pelvis swabs	Mg positivity
Simms et al (2003) [24]	UK	Case–control	Cases: PIDinbothGUMclinicsand hospital O&G clinics. Controls: undergoing bilateral tubal ligation in O&G clinics	GUM clinics and O&G clinics	Hager's criteria	Endocervical swabs	Mg-PID association and Mg positivity
Cohen et al (2002) [18]	Kenya	Case-control	Women presenting with low abdominal pain for 14 d or less	STI clinic	Endometritis	Endometrial biopsies	Mg-PID association and Mg positivity

Guidelines for clinical diagnosis of PID:

BASHH criteria for PID: lower abdominal tenderness, usually bilateral, adnexal tenderness, cervical motion tenderness and fever (>38°C) [5].

CDC criteria for PID: Three minimum clinical criteria are present on pelvic examination: cervical motion tenderness, uterine tenderness, or adnexal tenderness [7].

European STI management guideline: lower abdominal tenderness, adnexal tenderness on bimanual vaginal examination, cervical motion tenderness on bimanual vaginal examination, fever (>38.C) [12].

Australian STI guideline: Cervical motion tenderness and adnexal or uterine tenderness. Additional: cervical mucopurulent discharge [4].

Hager's criteria: lower abdominal pain, adnexal tenderness, and tenderness with motion of the cervix and uterus [11].

Abbreviations: BASHH, British Association for Sexual Health and HIV; CDC, Centers for Disease Control and Prevention; GIFT, GYN Infections Follow-Through Study; GUM, genitourinary medicine; Mg, *M. genitalium*; O&G, obstetrics and gynecology; PID, pelvic inflammatory disease; RCOG, Royal college of obstetrics and gynecology; RCT, randomized control trial; STI, sexually transmitted infection.

[a]Author contacted and confirmed sample type.

[b]Author contacted and confirm the criteria used to diagnose PID.

[c]Adjusted odds ratio (adjusted for age and *Chlamydia*).

[d]Adjusted odds ratio (adjusted for age, *Chlamydia*, self-reported partner treatment, sex between visits).

In subgroup analyses, the highest positivity estimate came from the Americas and the lowest estimate from the European region which did not differ from the Western Pacific. Importantly, specific geographical regions were not represented, including Southeast Asian and Eastern Mediterranean Regions, highlighting the need for more global data. In addition, we found that studies conducted in a mixed setting (outpatient/inpatient/emergency department) where women with more severe PID symptoms are likely to attend, had the highest positivity for *M. genitalium* in PID. Finally, women with PID with a higher epidemiological risk of STIs had a higher pooled positivity for *M. genitalium* compared to women at lower risk of STIs. These data indicate that the burden of *M. genitalium* in PID may be highest among individuals at higher epidemiological risk of STIs and in clinical settings more likely to be attended by those with more marked symptoms.

An accurate diagnosis of PID is difficult in the outpatient setting because of the wide spectrum of clinical presentations and varying levels of expertise. This is likely to have contributed to difficulties in understanding the true association between *M. genitalium* and PID. The "gold standard" test is laparoscopy, but laparoscopy is invasive, costly, and requires expertise. As such laparoscopy is not undertaken for mild to moderate cases of PID that present to sexual health and community services. Current international guidelines for diagnosing PID prioritize the use of clinical criteria that are sensitive but not specific and include, at a minimum, the presence of pelvic organ tenderness in the absence of competing diagnoses [4–7, 12]. In an attempt to generate robust estimates, we only included studies that used established and accepted clinical criteria for the diagnosis of PID or provided histological or laparoscopic confirmation of endometritis/salpingitis. Studies with missing or unclear information on PID diagnosis were excluded from the analysis which reduced the number of eligible studies but increased the validity of the outcome measure.

PID is a condition with a polymicrobial etiology, and most international guidelines recommend treating PID cases empirically with broad spectrum antibiotics including doxycycline in an outpatient setting [7]. Although doxycycline may have some activity against *M. genitalium* (20%–30% microbial cure), it is not highly

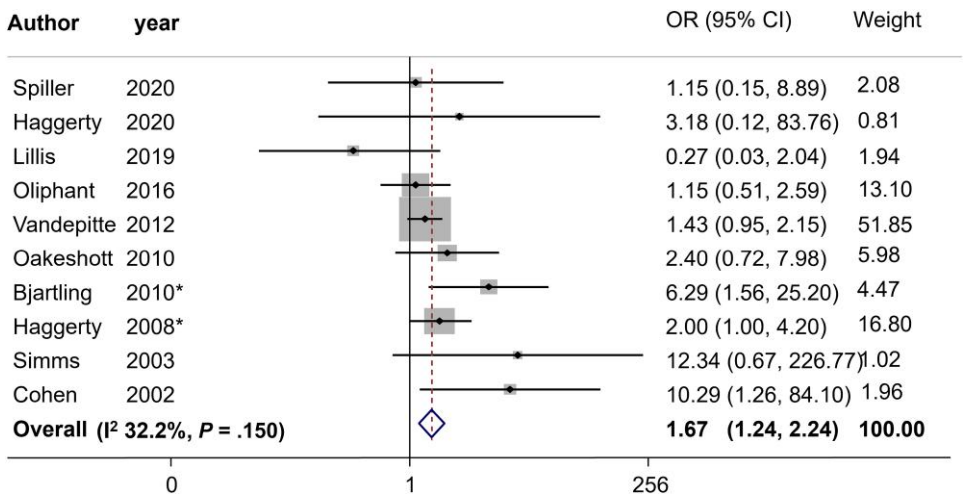

Figure 2. Forest plot of the association between *Mycoplasma genitalium* and PID cases. *Published odds ratio. Dotted line represents pooled OR. Weights are from Random effects model. Abbreviations: CI, confidence interval; OR, odds ratio; PID, pelvic inflammatory disease.

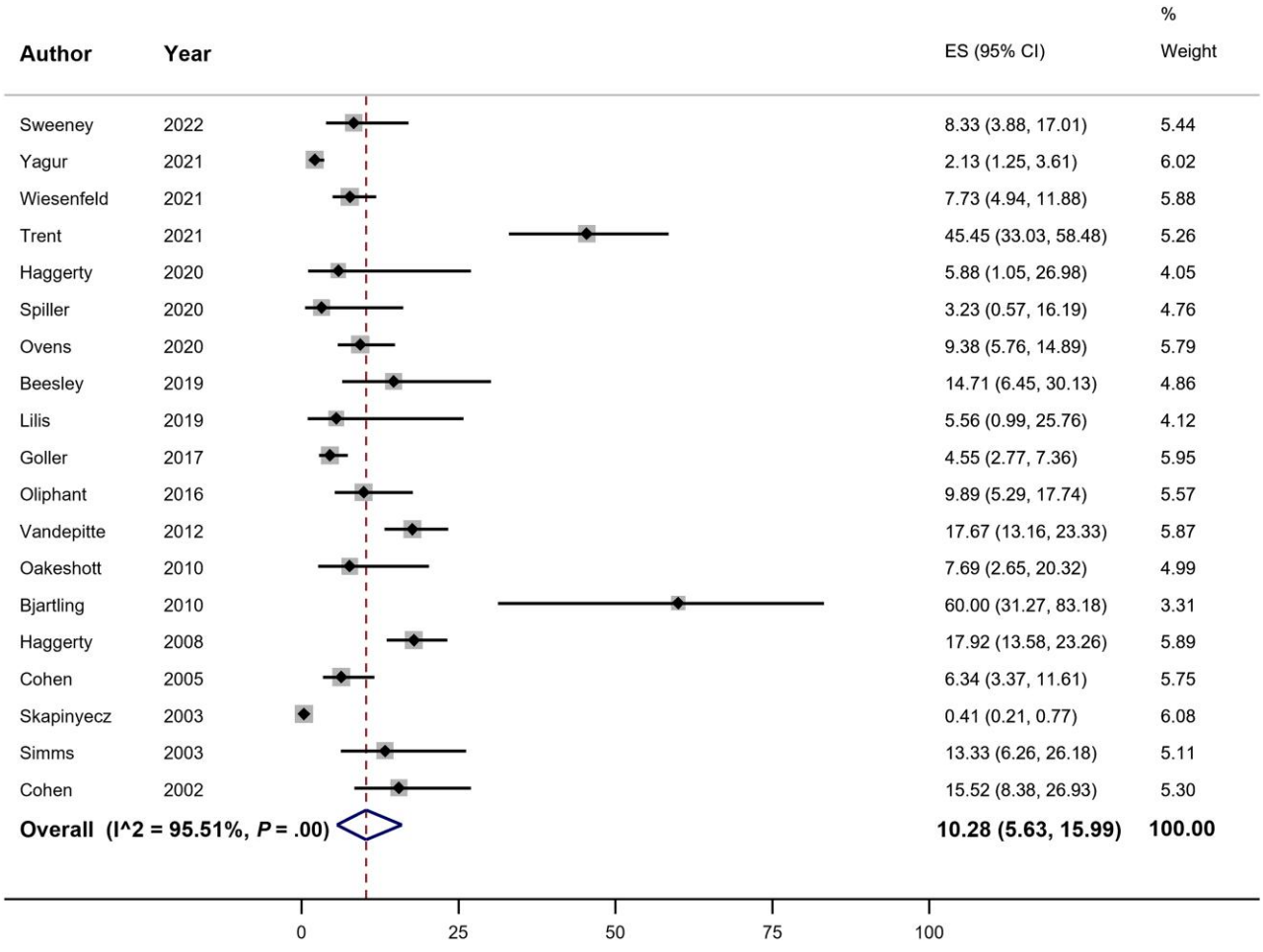

Figure 3. Forest plot of *Mycoplasma genitalium* positivity within PID cases. Dotted line represents -pooled *M. genitalium* positivity in PID. Abbreviations: CI, confidence interval; ES, effect size; PID, pelvic inflammatory disease.

effective in eradicating *M. genitalium*, and many guidelines recommend the use of moxifloxacin for 14 days if *M. genitalium* is detected [39]. *M. genitalium* may also persist in endometrial tissue following empiric PID treatment that does not effectively treat *M. genitalium* [20, 40]. A recent study demonstrated that the inclusion of metronidazole in addition to ceftriaxone and doxycycline resulted in a modest and unexpected increase in microbial cure for PID cases with *M. genitalium* detected compared to ceftriaxone and doxycycline alone. Interestingly, nitroimidazoles have now been shown to have some efficacy against *M. genitalium* in vitro [41]. Clearly, further studies examining the efficacy of nitroimidazoles for *M. genitalium* are needed. Curing *M. genitalium* is becoming increasingly challenging due to rising resistance to our commonly used antibiotics [42]; although resistance assays improve antimicrobial stewardship and cure [43], clinicians are increasingly encountering untreatable infections, which in the case of PID can be highly problematic.

The strengths of this meta-analysis are that we only included studies that required established clinical criteria to diagnose PID and a NAAT to detect *M. genitalium*. Limitations include the fact that data predominantly came from high income countries, and there were few studies from low- and middle-income countries (n = 3) [18, 26, 28], although the biologic mechanism by which *M. genitalium* may cause PID is not expected to vary geographically. Our eligibility criteria were limited to studies written in the English language, which may also have excluded studies of some populations. There was substantial heterogeneity in the pooled estimate of *M. genitalium* positivity among women with PID, but we could not attribute WHO geographic region, clinic setting, nor population grouping to the majority of the heterogeneity observed. In a sensitivity analysis that removed 4 outlier studies, the overall pooled estimate did not significantly vary. Finally, our pooled estimates came from mostly cross-sectional studies, highlighting that high quality, well-designed prospective studies are needed to further interrogate the temporal association between *M. genitalium* and PID.

In summary, our meta-analysis provides contemporary evidence that *M. genitalium* is associated with 67% increased odds of PID. It also showed that *M. genitalium* is not rare in PID, being detected in about 1 of 10 PID diagnoses. As international studies are reporting a decline in the proportion of PID cases attributed to traditional pathogens such as chlamydia and gonorrhea [44, 45], clinicians need to be aware that *M. genitalium* is a cause of PID and is not uncommon. Failure to respond to empiric treatment should at the very least alert clinicians to the need to test for *M. genitalium*, and where resources allow testing for chlamydia and gonorrhea at initial PID diagnosis, *M. genitalium* should also be included, as is currently recommended by a number of guidelines [4–6, 12].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors thank the following authors for providing additional information: Dr Sally Sweeny, Dr Rick Verma, Dr Yael Yagur, Dr Caroline Thng, Dr Jacques Pépin, and Dr Maeva Lefebvre.

Statement of data availability. Data available in the supplementary materials.

Financial support. K. H. was supported by an Australian Government Department of Higher Education Research Training Scholarship and Royal Australasian College of Physician Research Entry Scholarship. C. S. B. is supported by National Health and Medical Research Council (NHMRC) Leadership Investigator grant (grant number 1173361). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Potential conflicts of interest. L. M. declares payments to her institution for investigator-initiated research from Hologic, Inc., and Nabriva Therapeutics. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Ross J. Pelvic inflammatory disease. BMJ **2001**; 322:658–9.
2. Goller J, Fairley C, Guy R, et al. Aetiology of infections associated with 1228 cases of pelvic inflammatory disease in an urban Australian sexual health clinic setting. Sex Transm Dis **2014**; 1:S59.
3. Lis R, Rowhani-Rahbar A, Manhart LE. *Mycoplasma genitalium* infection and female reproductive tract disease: a meta-analysis. Clin Infect Dis **2015**; 61:418–26.
4. Australian sexually transmitted infection (STI) management guidelines (AUS). Australian sexually transmitted infection (STI) management guidelines for use in primary care 2022 update. Sex Health 2023 Feb [cited 20 1]; 2022/11/11:[1–8]. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36356948. Accessed 8 December 2023.
5. British Association for Sexual Health and HIV (BASHH). Pelvic inflammatory disease management guideline. 2019 [cited 2023 6th December 2023]; Available at: https://www.bashh.org/guidelines. Accessed 8 December 2023.
6. Worth Health Organisatin (WHO), Guidelines for the management of symptomatic sexually transmitted infections. Geneva: World Health Organization; 2021. 2021. Accessed 8 December 2023.
7. Centers for Disease Control and Prevention (CDC). Sexually Transmitted Infections Treatment Guidelines, 2021. [Guidelines] 2021 12/09/2023]; Available at: https://www.cdc.gov/std/treatment-guidelines/pid.htm. Accessed 8 December 2023.
8. Yusuf H, Trent M. Management of pelvic inflammatory disease in clinical practice. Ther Clin Risk Manag **2023**; 19:183–92.
9. Wiesenfeld HC, Meyn LA, Darville T, Macio IS, Hillier SL. A randomized controlled trial of ceftriaxone and doxycycline, with or without metronidazole, for the treatment of acute pelvic inflammatory disease. Clin Infect Dis **2021**; 72: 1181–9.
10. Page MJ, McKenzie JE, Bossuyt PM, et al. [The PRISMA 2020 statement: an updated guideline for reporting systematic reviewsDeclaracion PRISMA 2020: una guia actualizada para la publicacion de revisiones sistematicas]. Rev Panam Salud Publica **2022**; 46:e112.
11. Hager WD, Eschenbach DA, Spence MR, Sweet RL. Criteria for diagnosis and grading of salpingitis. Obstet Gynecol **1983**; 61:113–4.
12. Guideline for the management of pelvic inflammatory disease (European). 2017 European guideline for the management of pelvic inflammatory disease. Int J STD AIDS **2018**; 29:108–14.
13. Mathias Harrer PC, Furukawa TA, Ebert DD. Between-Study heterogeneity. In: Doing meta-analysis with R: a hands-on guide. Boca Raton, Florida; London, England, New York: CRC Press, **2021**:34.
14. Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol **2012**; 65:934–9.
15. Skapinyecz J, Smid I, Juhász A, et al. Planning of empirical antibiotic therapy for women with pelvic inflammatory diseases: a geographical area-specific study. Eur J Obstet Gynecol Reprod Biol **2003**; 111:183–8.
16. Trent M, Perin J, Rowell J, et al. Using innovation to address adolescent and young adult health disparities in pelvic inflammatory disease: design of the

Technology Enhanced Community Health Precision Nursing (TECH-PN) trial. Journal of Infectious Diseases **2021**; 224(12 Suppl 2):S145–51.
17. Bjartling C, Osser S, Persson K. The association between *Mycoplasma genitalium* and pelvic inflammatory disease after termination of pregnancy. Bjog **2010**; 117: 361–4.
18. Cohen CR, Manhart LE, Bukusi EA, et al. Association between *Mycoplasma genitalium* and acute endometritis. Lancet **2002**; 359:765–6.
19. Haggerty CL, Ness RB, Totten PA, et al. Presence and concentrations of select bacterial vaginosis-associated bacteria are associated with increased risk of pelvic inflammatory disease. Sex Transm Dis **2020**; 47:344–6.
20. Haggerty CL, Totten PA, Astete SG, et al. Failure of cefoxitin and doxycycline to eradicate endometrial *Mycoplasma genitalium* and the consequence for clinical cure of pelvic inflammatory disease. Sex Transm Infect **2008**; 84:338–42.
21. Lillis RA, Martin DH, Nsuami MJ. *Mycoplasma genitalium* infections in women attending a sexually transmitted disease clinic in New Orleans. Clinical Infectious Diseases **2019**; 69:459–65.
22. Oakeshott P, Aghaizu A, Hay P, et al. Is *Mycoplasma genitalium* in women the "new *Chlamydia*?" A community-based prospective cohort study. Clin Infect Dis **2010**; 51:1160–6.
23. Oliphant J, Azariah S. Pelvic inflammatory disease associated with *Chlamydia trachomatis* but not *Mycoplasma genitalium* in New Zealand. Sex Health **2016**; 13: 43–8.
24. Simms I, Eastick K, Mallinson H, et al. Associations between *Mycoplasma genitalium*, *Chlamydia trachomatis*, and pelvic inflammatory disease. Sex Transm Infect **2003**; 79:154–6.
25. Spiller OB, Rees CL, Morris DJ, Davies RL, Jones LC. *Mycoplasma genitalium* prevalence in Welsh sexual health patients: low antimicrobial resistance markers and no association of symptoms to bacterial load. Microb Pathog **2020**; 139: 103872.
26. Vandepitte J, Bukenya J, Hughes P, et al. Clinical characteristics associated with *Mycoplasma genitalium* infection among women at high risk of HIV and other STI in Uganda. Sex Transm Dis **2012**; 39:487–91.
27. Beesley V, Thng C. Testing for *Mycoplasma genitalium* in pelvic inflammatory disease: a clinical audit. Aust N Z J Obstet Gynaecol **2019**; 4:826–9.
28. Cohen CR, Mugo NR, Astete SG, et al. Detection of *Mycoplasma genitalium* in women with laparoscopically diagnosed acute salpingitis. Sex Transm Infect **2005**; 81:463–6.
29. Goller JL, De Livera AM, Fairley CK, et al. Characteristics of pelvic inflammatory disease where no sexually transmitted infection is identified: a cross-sectional analysis of routinely collected sexual health clinic data. Sex Transm Infect **2017**; 93:68–70.
30. Ovens KJ, Reynolds-Wright JJ, Cross ELA, et al. High rates of treatment failure for *Mycoplasma genitalium* among men and women attending a sexual health clinic. BMJ Sex Reprod Health **2020**; 46:132–8.
31. Sweeney S, Bateson D, Fleming K, Huston W. Factors associated with pelvic inflammatory disease: a case series analysis of family planning clinic data. Womens Health (Lond) **2022**; 18:17455057221112263.
32. Yagur Y, Weitzner O, Barchilon Tiosano L, et al. Characteristics of pelvic inflammatory disease caused by sexually transmitted disease—an epidemiologic study. J Gynecol Obstet Hum Reprod **2021**; 50:102176.
33. Cina M, Baumann L, Egli-Gany D, et al. *Mycoplasma genitalium* incidence, persistence, concordance between partners and progression: systematic review and meta-analysis. Sex Transm Infect **2019**; 95:328–35.
34. Baumann L, Cina M, Egli-Gany D, et al. Prevalence of *Mycoplasma genitalium* in different population groups: systematic review andmeta-analysis. Sex Transm Infect **2018**; 94:255–62.
35. Sonnenberg P, Ison CA, Clifton S, et al. Epidemiology of *Mycoplasma genitalium* in British men and women aged 16–44 years: evidence from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). Int J Epidemiol **2015**; 44: 1982–94.
36. Torrone EA, Kruszon-Moran D, Philips C, et al. Prevalence of urogenital *Mycoplasma genitalium* infection, United States, 2017 to 2018. Sex Transm Dis **2021**; 48:e160–2.
37. Menezes ME, Silver EJ, Goldstein DY, et al. Prevalence and factors associated with *Mycoplasma genitalium* infection in at-risk female adolescents in Bronx county, New York. Sex Transm Dis **2023**; 50:635–41.
38. Price MJ, Ades AE, De Angelis D, et al. Risk of pelvic inflammatory disease following *Chlamydia trachomatis* infection: analysis of prospective studies with a multistate model. Am J Epidemiol **2013**; 178:484–92.
39. Ross, J.D., H.S. Cronje, T. Paszkowski, et al., Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial. Sex Transm Infect, **2006**. 82: p. 446–51.
40. Trent, M., H.E. Yusuf, J. Perin, et al., Clearance of *Mycoplasma genitalium* and *Trichomonas vaginalis* among adolescents and young adults with pelvic inflammatory disease: results from the tech-N study. Sex Transm Dis, **2020**. 47: p. e47–50.
41. Wood GE, Kim CM, Aguila LKT, Cichewicz RH. In vitro susceptibility and resistance of *Mycoplasma genitalium* to nitroimidazoles. Antimicrob Agents Chemother **2023**; 67:e0000623.
42. Machalek DA, Tao Y, Shilling H, et al. Prevalence of mutations associated with resistance to macrolides and fluoroquinolones in *Mycoplasma genitalium*: a systematic review and meta-analysis. Lancet Infect Dis **2020**; 20:1302–14.
43. Read TRH, Fairley CK, Murray GL, et al. Outcomes of resistance-guided sequential treatment of *Mycoplasma genitalium* infections: a prospective evaluation. Clin Infect Dis **2019**; 68:554–60.
44. Moore MS, Golden MR, Scholes D, Kerani RP. Assessing trends in *Chlamydia* positivity and gonorrhea incidence and their associations with the incidence of pelvic inflammatory disease and ectopic pregnancy in Washington state, 1988–2010. Sex Transm Dis **2016**; 43:2–8.
45. Owusu-Edusei K Jr, Bohm MK, Chesson HW, Kent CK. *Chlamydia* screening and pelvic inflammatory disease: insights from exploratory time-series analyses. Am J Prev Med **2010**; 38:652–7.